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Palladium-Catalysed Arylative Cyclisation of *N*-Allylacetamides with Aryl Halides Yielding Benzyl-Substituted Oxazolines

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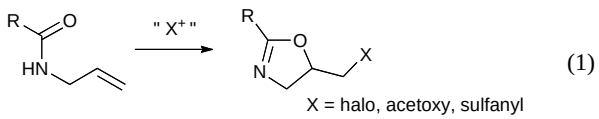
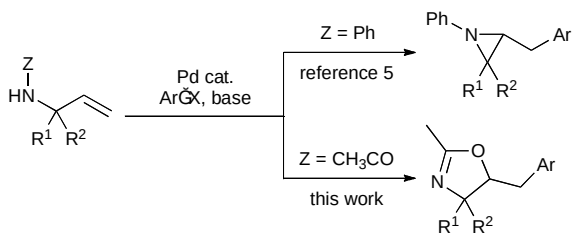
Treatment of *N*-allylacetamide with aryl halide in the presence of sodium *t*-butoxide and a palladium catalyst leads to arylative cyclisation to provide the corresponding benzyl-substituted oxazoline in high yield.

Oxazoline is an important skeleton often found in biologically interesting molecules,[1] synthetic intermediates,[2] and ligands for transition metal complexes.[3] Oxazolines are usually prepared from carboxylic acid derivatives and β-aminoalcohols.[2a,2b] Oxidative cyclisation of *N*-allylamides is also a useful route to oxazolines since the oxazolines thus formed can possess a functionalised side chain at the 5-position (eq 1).[4]



(1)

We have developed palladium-catalysed intramolecular arylative cyclisation reactions of *N*-allylanilines with aryl halides to yield aziridines (Scheme 1, Z = Ph).[5] During the course of the study, we found that a similar reaction of *N*-allylacetamides resulted in the selective formation of 5-benzyl-substituted oxazolines without contamination by the corresponding aziridines (Scheme 1, Z = CH_3CO). Here we report the preliminary results of the arylative cyclisation for the synthesis of oxazolines.[6,7] This is regarded as a

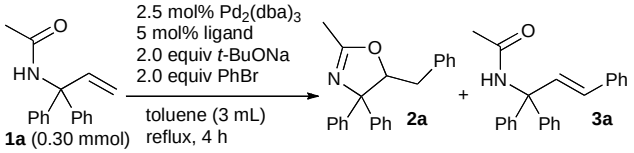


Scheme 1. Palladium-catalysed reactions of allylamine derivatives with aryl halides

new variant of the carboetherification reactions that Wolfe and others recently developed to construct tetrahydrofuran derivatives.[8]

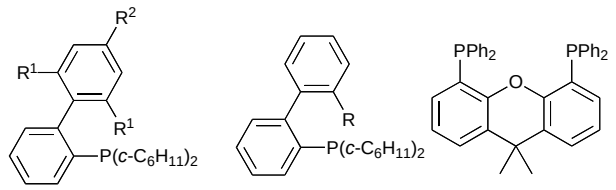
Treatment of *N*-allylacetamide **1a** with bromobenzene under the same conditions as reported previously[5] afforded benzyl-substituted oxazoline **2a** in 75% yield (Table 1, entry 1). The cyclisation reaction inevitably competed with the Mizoroki-Heck reaction, which yielded **3a** as the only identifiable byproduct. Several ligands were screened (Figure 1), and bulky ligands are generally effective for the cyclisation. SPhos and RuPhos are excellent (entries 1 and 2), while larger XPhos showed no activity for the cyclisation (entry 3). Other biphenylyl phosphines are less effective (entries 4 and 5). Xantphos and tri-*t*-butylphosphine were inferior in terms of **2a**/**3a** selectivity (entries 6 and 7). After further fine tuning, the use of SPhos with smaller amounts of *t*-BuONa, PhBr, and toluene proved to be the best conditions in terms of both yield of **2a** and **2a**/**3a** ratio. (entry 8).[9] The choice of sodium *t*-butoxide is crucial. The use of sodium methoxide, sodium hydroxide, potassium *t*-butoxide, potassium carbonate, or caesium carbonate resulted in exclusive formation of **3a**.[10,11] Although other amides such as benzamide could undergo similar transformations, yields of the corresponding oxazolines were much lower, up to 30%.

Table 1. Effect of ligands on palladium-catalysed phenylative cyclisation reaction of **1a** and competitive Mizoroki-Heck reaction



entry	ligand[a]	**2a** /%	**3a** /%
1	SPhos	75	16
2	RuPhos	78	19
3	XPhos	0	45
4	DavePhos	55	25
5	P1	12	21
6	Xantphos	76	24
7	*t*-Bu_3P	70	30
8[b]	SPhos	76	12

[a] See Figure 1. [b] 1.5 equiv of *t*-BuONa, 1.2 equiv of PhBr, and 1.5 mL of toluene were used.



SPhos: R^1 = OMe, R^2 = H
RuPhos: R^1 = O-*i*-Pr, R^2 = H
XPhos: R^1 = R^2 = *i*-Pr
DavePhos: R = NMe_2
P1: R = H
Xantphos

Figure 1. Structures of ligands

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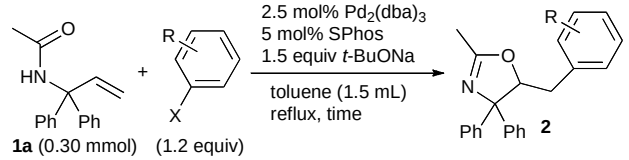
†Electronic supplementary information (ESI) available: Characterization data. See, DOI:.....

The scope of aryl halides is summarised in Table 2. Aryl chlorides as well as aryl bromides participated in the reaction (entries 1, 7, and 8). Sterically demanding aryl bromides reacted smoothly (entries 2, 3, and 10). Electron-deficient fluorinated aryl bromides were also reactive (entries 4 and 5). Aryl halides bearing a *t*-butoxycarbonyl, diethylaminocarbonyl, or cyano group underwent the arylative cyclisation to yield the corresponding products in good yields (entries 6–8). The reaction of **1a** with electron-rich 4-bromoanisole resulted in modest yield of **2i** and formation of a significant amount of Mizoroki-Heck byproduct (entry 9). On the other hand, the steric hindrance of 2-bromoanisole is likely to retard the side reaction (entry 10). It is worth noting that separation of **2** from **3** was readily performed on silica gel in each case.[9]

Table 2. Scope of aryl halides



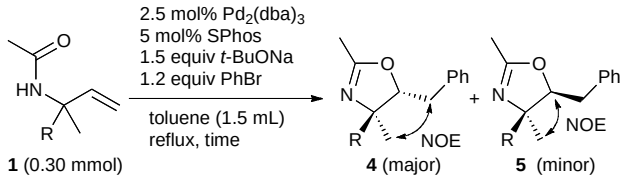
1a (0.30 mmol) (1.2 equiv)

entry	R	X	time /h	2	yield /%[a]
1	H	Cl	4	**2a**	77 (7)
2[b]	2-Me	Br	4	**2b**	84 (5)
3[b]	(1-naphthyl)	Br	6	**2c**	79 (6)
4	4-F	Br	8	**2d**	76 (6)
5	4-CF_3	Br	8	**2e**	80 (4)
6	4-CO_2-*t*-Bu	Br	12	**2f**	61 (6)
7	4-$CONEt_2$	Cl	10	**2g**	67 (15)
8	4-CN	Cl	10	**2h**	59 (3)
9	4-MeO	Br	10	**2i**	50 (24)
10	2-MeO	Br	8	**2j**	69 (9)

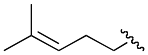
[a] Isolated yields of **2**. The NMR yields of the corresponding Mizoroki-Heck byproducts are in parentheses. The byproducts were easily separable from **2** by chromatographic purification. [b] RuPhos was used instead of SPhos.

Several *N*-allylacetamides that bear a stereogenic center at the allylic position were prepared and subjected to the arylative cyclisation reaction (Table 3). The reactions proceeded smoothly with good diastreoselectivity. The major isomers have the larger R group and the newly formed benzyl group in a trans relationship. The relative stereochemistries of **4** and **5** were determined by NOE analysis.

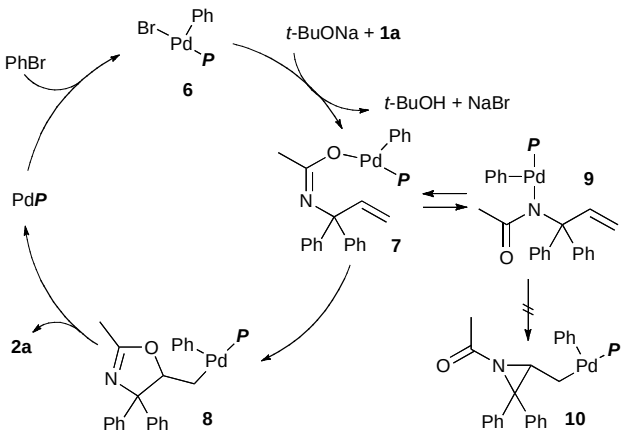
Table 3. Diastereoselective cyclisation



1 (0.30 mmol)

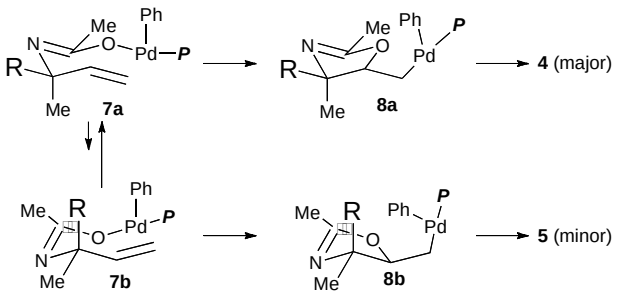
entry	1	R	time /h	yield /%	4/5
1	**1b**	Ph	10	61	**4b/5b** = 73:27
2	**1c**	1-naphthyl	12	68	**4c/5c** = 84:16
3	**1d**		10	66	**4d/5d** = 73:27

Based on the previous results,[5,8] a plausible reaction mechanism is outlined in Scheme 2. Oxidative addition is followed by exchange between the bromide and amide **1a** to yield **7**. Intermediate **7** would undergo intramolecular oxypalladation to give **8**. Smooth reductive elimination with the aid of the bulky phosphine ligand affords product **2a** and regenerates the initial palladium species. There can be an equilibrium between **7** and palladium amide **9**. However, cyclisation of **9** that forms an aziridine skeleton could not occur.



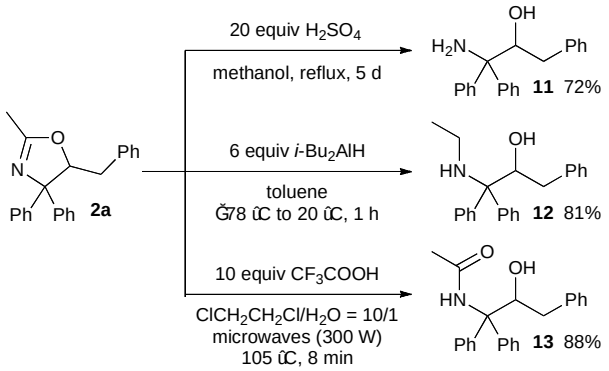
Scheme 2. Plausible reaction mechanism

The stereoselectivity is rationalised by considering that the larger R group would prefer locating at the pseudoequatorial position prior to cyclisation (Scheme 3). Intermediate **7a** would be thus more stable than **7b**, and the formation of oxazoline **8a** predominated to lead to **4** with high diastereoselectivity.



Scheme 3. Origin of Stereoselectivity

Finally, transformation of oxazoline **2a** was examined (Scheme 4). Methanolysis of **2a** occurred under acidic conditions[12] to yield amino alcohol **11**. Reduction of **2a** with diisobutylaluminum hydride provided *N*-ethyl amino alcohol **12**. Oxazoline **2a** was converted to acetamide **13** by acidic hydrolysis with trifluoroacetic acid.[13] The overall transformation of **1a** to **13** represents regioselective carbohydroxylation of *N*-allylacetamide.



Scheme 4. Transformation of oxazoline **2a**

In summary, we have developed palladium-catalysed carboetherification reactions of *N*-allylacetamides with aryl halides. The reactions provided benzyl-substituted oxazolines without the conceivable formation of aziridines.[5] In light of the importance of oxazolines, the method offers a useful tool in organic synthesis. Pursuing higher diastereoselectivity and asymmetric cyclization and mechanistic studies are underway.

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9 Experimental Procedure: Sodium *t*-butoxide (43 mg, 0.45 mmol) was added to a 30–mL two-necked reaction flask equipped with a Dimroth condenser and was dried in vacuo with heating by a hair dryer for 1 min. Tris(dibenzylideneacetone)dipalladium (6.9 mg, 0.0075 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 6.2 mg, 0.015 mmol) were added to the flask, and the flask was filled with argon by using the standard Schlenck technique. Toluene (0.5 mL) was then added at room temperature. After the suspension was stirred for 10 min, a mixture of **1a** (75.4 mg, 0.30 mmol) and bromobenzene (56.5 mg, 0.36 mmol) dissolved in toluene (1.0 mL) was added to the flask at ambient temperature. The mixture was heated at reflux for 4 h with an oil bath. After the flask was cooled to room temperature, water (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate three times. The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/AcOEt = 3/1) to provide 5-benzyl-2-methyl-4,4-diphenyl-4,5-dihydrooxazole **2a** (74.7 mg, 0.228 mmol, 76%, R_f = 0.37). *N*-Cinnamylacetamide **3a** appeared at R_f = 0.20 (hexane/AcOEt = 3/1). IR (nujol) 3024, 1665, 1448, 1258, 973, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.32 (dd, *J* = 15.0, 11.0 Hz, 1H), 2.57 (dd, *J* = 15.0, 2.5 Hz, 1H), 5.34 (dd, *J* = 11.0, 2.5 Hz, 1H), 7.15–7.20 (m, 4H), 7.21–7.34 (m, 7H), 7.35–7.40 (m, 2H), 7.44–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.64, 39.81, 81.07, 88.45, 126.76, 127.11, 127.39, 127.45, 128.16, 128.18, 128.64, 128.73, 129.21, 138.60, 142.14, 145.78, 164.15; Found: C, 84.12; H, 6.58%. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46%. m.p. 116.0–117.5 ˚C.

10 Exposure of **3a** to the reaction conditions resulted in no reaction. This result strongly suggests that **3a** is not an intermediate en route to **2a**.

11 When the reaction was performed in the presence of silver salts, yield of **2a** was not improved.

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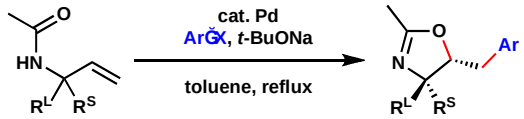
TOC Graphics



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